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## The Obesity and Heart Failure Epidemics Among African Americans: Insights From the Jackson Heart Study

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### Abstract

**Background**—Higher rates of obesity and heart failure have been observed in African Americans, but associations with mortality are not well described. We examined intermediate-and long-term clinical implications of obesity in African Americans and associations between obesity and all-cause mortality, heart failure, and heart failure hospitalization.

**Methods and Results**—We conducted a retrospective analysis of a community sample of 5292 African Americans participating in the Jackson Heart Study between September 2000 and January 2013. The main outcomes were associations between BMI and all-cause mortality at 9 years and heart failure hospitalization at 7 years using Cox proportional hazards models and interval development of heart failure (median 8 years follow-up) using a modified Poisson model. At baseline, 1406 (27%) participants were obese and 1416 (27%) were morbidly obese. With increasing BMI, the cumulative incidence of mortality decreased ( $P = .007$ ), whereas heart failure increased ( $P < .001$ ). Heart failure hospitalization was more common among morbidly obese

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participants (9.0%; 95% CI, 7.6–11.7) than among normal-weight patients (6.3%; 95% CI, 4.7–8.4). After risk adjustment, BMI was not associated with mortality. Each 1-point increase in BMI was associated with a 5% increase in the risk of heart failure (HR, 1.05; 95% CI, 1.03–1.06;  $P < .001$ ) and the risk of heart failure hospitalization for BMI greater than 32 kg/m<sup>2</sup> (HR, 1.05; 95% CI, 1.03–1.07;  $P < .001$ ).

**Conclusions**—Obesity and morbid obesity were common in a community sample of African Americans, and both were associated with increased heart failure and heart failure hospitalization.

## Introduction

The association of obesity with heart failure (HF) has not been well described in African Americans (AAs), who have higher rates of both obesity and HF than white populations.[1, 2] The relationship between obesity in AAs and mortality also remains unclear. Some studies have suggested a paradoxical lower risk of death in AAs with obesity compared with other populations with obesity.[3–9] To better understand associations between obesity and health outcomes among AAs, we examined relationships between BMI and all-cause mortality, prevalent HF at interval follow-up examinations, and HF hospitalization among more than 5000 participants in the Jackson Heart Study.[10–14] We hypothesized that obesity would be common in this cohort and that higher BMI would be associated with greater risks of mortality, prevalent HF, and hospitalization for HF.

## Methods

### Data Sources

The Jackson Heart Study is a prospective, community-based, observational study initiated in 2000 to investigate risk factors for cardiovascular disease in AAs.[10] A strength of the study is that it is the largest cohort to date specifically examining African Americans and their risks for cardiovascular disease. All participants provided written informed consent, and study protocols were approved by local institutional review boards. The institutional review board of the Duke University Health System approved our study and the use of study data. Participants completed 3 study visits: exam 1 between September 2000 and March 2004, exam 2 between October 2005 and December 2008, and exam 3 between February 2009 and January 2013. The details of data collected and visit procedures have been described previously.[15] The Jackson Heart Study cohort surveillance system collects follow-up data on all participants, including deaths from 2000 through 2011 and HF hospitalizations from 2005 through 2011.[16]

### Study Population

For all outcomes, we included participants who completed exam 1 and had BMI measured. For the analysis of HF hospitalizations, we limited the cohort to participants who survived to January 1, 2005, when HF hospitalization surveillance began. For the assessment of all prevalent HF outcomes, we excluded participants with baseline HF at exam 1. We also required that participants completed exam 2 for the assessment of prevalent HF at exam 2, and we required completion of exam 3 for the assessment of prevalent HF at exam 3 (Supplemental Figure 1).

## Body Mass Index

The study variable of interest was baseline BMI. Height and weight were determined with the participant wearing an examination gown without shoes.[17] We assessed BMI on a continuous scale per 1 point and categorically as follows: normal weight (less than 25 kg/m<sup>2</sup>), overweight (25 to less than 30 kg/m<sup>2</sup>), obese (30 to less than 35 kg/m<sup>2</sup>), and morbidly obese (35 kg/m<sup>2</sup> or greater).

## Outcomes

The primary outcomes were all-cause mortality, prevalent HF at exam 2, prevalent HF at exam 3, and hospital admission for HF. Methods for identification of all-cause mortality in the cohort have been described previously.[16] We assessed all-cause mortality within 9 years after the exam 1 visit date based on a median follow-up time of 9 years and 75th percentile of 10 years. Since HF history was not collected at the 3 clinical exams, we derived prevalent HF at each exam using the modified Gothenburg criteria developed and validated in the ARIC data set and as recently applied to the Jackson Heart Study cohort.[18, 19] Among participants without prevalent HF at exam 1, we assessed prevalent HF at exam 2 (median follow-up, 4.8 years from exam 1; range, 3.4–8.2 years) and prevalent HF at exam 3 (median follow-up, 8.0 years from exam 1; range, 6.4–12.2 years). We also assessed the cumulative incidence of HF hospitalization between 2005 and 2011 among study participants who survived to January 1, 2005, when HF hospitalization surveillance began. (Median and 75th percentile follow-up was 7 years.) Potential HF hospitalizations in the cohort were identified and adjudicated as described previously.[16]

## Covariates

Variables from the baseline clinical exam included demographic characteristics, medical history, physical examination measurements, medications, laboratory test results, and cardiac test results. Medical history was based on either direct clinical examination, self-reported disease history, or health behaviors. For variables with less than 5% missingness, we imputed continuous variables to the overall median value, dichotomous variables to “no,” and multichotomous variables to the most frequent categorical value. For variables with greater than 5% missingness (medication variables), we treated the missing values as a separate category.

## Statistical Analysis

We describe exam 1 baseline characteristics of the study population by BMI category using frequencies with percentages for categorical variables and medians with interquartile ranges or means with SDs for continuous variables. We tested for differences between groups using chi-square tests for categorical variables and Kruskal-Wallis tests for continuous variables.

We calculated the cumulative incidence of all-cause mortality and HF hospitalization by BMI category using Kaplan-Meier estimates, and we tested for differences between groups using log-rank tests. For all survival analyses, we censored data at the time of participant loss to follow-up, or the end of study event surveillance follow-up (December 31, 2011). For HF hospitalization, we also censored data for participants at the time of death. For prevalent HF at exam 2 and prevalent HF at exam 3, we used frequencies with percentages, calculated

exact CIs for binomial proportions, and tested for differences between groups using Fisher exact tests.

We assessed the unadjusted and adjusted associations between continuous and categorical BMI and outcomes. We used Cox proportional hazards models for mortality and HF hospitalization outcomes. To examine associations with prevalent HF at exam 2, we used a modified Poisson model with an offset parameter to adjust for log of participant time between exam 1 and exam 2.[20, 21] We explored both linear and nonlinear functional forms for BMI, including polynomials, restricted cubic splines, and linear splines. To explore the middle and tails of the BMI distribution in our restricted cubic spline analyses, we selected 5 BMI knots at the 5th (22 kg/m<sup>2</sup>), 35th (28 kg/m<sup>2</sup>), 50th (30 kg/m<sup>2</sup>), 65th (33 kg/m<sup>2</sup>) and 95th (45 kg/m<sup>2</sup>) percentiles and chose the population median of 30 kg/m<sup>2</sup> as the reference category (hazard ratio, 1.00). To simplify interpretation, information gleaned from restricted cubic splines was then used to develop linear spline models with knots selected according to optimal model fit determined by the minimum Akaike information criterion.

We conducted 5 sensitivity analyses. First, we tested for interactions between BMI (categorical and continuous) and sex in all of multivariable models, because of previously observed associations with BMI and HF by sex.[22] Second, we repeated models replacing BMI with waist circumference as an alternative measure of obesity. Third, we excluded participants with a BMI less than 18.5 kg/m<sup>2</sup> (underweight participants with a potentially increased risk profile as compared with a BMI 18.5 to less than 25 kg/m<sup>2</sup>) and repeated the unadjusted and multivariable models. Fourth, we performed additional analyses with the addition of a categorical variable for average hours of self-reported weekly physical activity in the past year (none; <1 hour; 1–<2 hours; 2–<3 hours; 3–<4 hours; 4 hours). Finally, we explored potential metabolic and/or inflammatory mediators (ie, hypertension, diabetes and glucose, serum triglyceride, and C-reactive protein) on the causal pathway between BMI and outcomes. For each outcome, we ran 5 models to compare the effect of BMI after adjustment for age, sex, and the potential mediators and to assess possible over-adjustment bias.

We used a 2-tailed  $\alpha$  level of .05 to establish statistical significance, and we report 95% CIs. We used SAS version 9.3 (SAS Institute Inc) for all analyses.

## Results

Of 5301 participants who completed exam 1, we excluded 9 (0.1%) who had missing BMI data (Supplemental Figure 1). The analysis sample for all-cause mortality thus consisted of 5292 participants. For the analysis of HF hospitalization, we included all 5184 participants who survived to 2005. Table 1 shows the baseline characteristics of the 5292 participants who completed exam 1, stratified by categories of BMI. In the overall cohort, 769 (15%) had normal weight, 1701 (32%) were overweight, 1406 (27%) were obese, and 1416 (27%) were morbidly obese. Relatively few patients in the lowest BMI category had a BMI less than 18.5 kg/m<sup>2</sup> ( $n = 26/769$ ; 3%). Morbidly obese participants were the youngest group, and female sex and baseline HF were more common with increasing BMI.

Figure 1 shows the cumulative incidence of death within 9 years and HF hospitalization within 7 years after exam 1, stratified by categories of BMI. The observed incidence of mortality decreased as BMI increased ( $P = .007$ ). Supplemental Table 1 shows the frequency of prevalent HF at exam 2 (3 to 8 years after exam 1) and exam 3 (6 to 12 years after exam 1). We observed a significant difference in prevalent HF between groups at both exams 2 and 3, with increasing frequency of HF observed as BMI increased ( $P < .001$  for both comparisons). At exam 2, the number of participants having developed HF in each BMI category were as follows: 11 in the normal weight, 34 in the overweight, 41 in the obese, and 81 in the morbidly obese. At exam 3, 12 normal weight participants developed HF, 43 participants in the overweight category, 61 in the obese, and 98 in the morbidly obese. There was a significant difference in HF hospitalization between groups ( $P = .008$ ), with the highest rate in morbidly obese participants of 9.0% (95% CI, 7.6–11.7) and the lowest rate in obese participants of 5.9% (95% CI, 4.8–7.4).

Table 2 shows the associations between BMI and the outcomes of all-cause mortality, prevalent HF at exam 2, prevalent HF at exam 3, and HF hospitalization. In both unadjusted and adjusted analyses of all-cause mortality, increasing BMI per 1 point was not associated with a statistically significant greater risk ( $P = .08$  and  $P = .41$ ). We further explored the adjusted association of continuous BMI and all-cause mortality using restricted cubic splines with the population median BMI of 30 kg/m<sup>2</sup> as the reference category (Supplemental Figure 2A). The Wald chi-square test for nonlinear association was significant ( $P < .001$ ). We also performed the unadjusted and adjusted analyses of associations between linear BMI splines and all-cause mortality with knots selected according to optimal model fit (Figure 2A; Supplemental Table 2). For each 1-point increase in BMI up to 27 kg/m<sup>2</sup>, the adjusted hazard of all-cause mortality decreased by 9%. However, there was no statistically significant association with mortality per 1 point increase in BMI greater than 27 kg/m<sup>2</sup> ( $P = .22$ ). In the categorical comparison with normal-weight participants, the multivariable adjusted risk of all-cause mortality was 34% lower in the overweight group, 30% lower in the obese group, and 34% lower in the morbidly obese group.

In multivariable adjusted analyses of prevalent HF, each 1-point increase in BMI was associated with a 6% increase in HF measured at exam 2 and a 5% increase at exam 3. In restricted cubic spline analyses, the Wald chi-square test for nonlinearity was not significant for HF at exam 2 ( $P = .14$ ; Supplemental Figure 2B) or HF at exam 3 ( $P = .06$ ; Supplemental Figure 2C). In the adjusted categorical comparison to participants with normal BMI, only morbidly obese participants had a higher risk of HF at exam 2 ( $P < .001$ ). At exam 3, both obese ( $P = .009$ ) and morbidly obese ( $P < .001$ ) participants had higher risks of HF compared with participants with normal BMI.

After multivariable adjustment, each 1-point increase in BMI was associated with a 2% higher hazard of HF hospitalization ( $P = .007$ ). We further explored the adjusted association of continuous BMI and HF hospitalization using restricted cubic splines (Supplemental Figure 2D). The graph suggests an increased hazard of HF hospitalization per increasing BMI only above the median, and the Wald chi-square test for overall nonlinear association was significant ( $P = .003$ ). We also examined the unadjusted and adjusted associations between linear BMI splines and HF hospitalization (Figure 2B; Supplemental Table 2). For

each 1-point increase in BMI up to 32 kg/m<sup>2</sup>, the adjusted hazard of HF hospitalization decreased by 4% ( $P = .03$ ). However, with BMI greater than 32, each 1-point increase in BMI was associated with a 5% higher hazard of HF hospitalization ( $P < .001$ ). In the unadjusted categorical comparison to normal-weight participants, only morbidly obese participants had a higher hazard of HF hospitalization ( $P = .04$ ), but the association did not remain significant after multivariable adjustment.

In sensitivity analyses, we observed no significant interaction between sex and BMI. Substitution of waist circumference for BMI did not change the direction or magnitude of observed associations with outcomes. Exclusion of participants with a BMI less than 18.5 kg/m<sup>2</sup> also did not change the direction of the observed associations with outcomes (Supplemental Table 3). Addition of self-reported physical activity as a covariate similarly led to nearly identical results as in the original models. Finally, the addition of potential metabolic and/or inflammatory mediators to age- and sex-adjusted models resulted in minimal change in the adjusted associations between continuous BMI and outcomes (Supplemental Table 4).

## Discussion

### Main findings

In this analysis of a community-based sample of AAs, obesity and morbid obesity were common; obesity and morbid obesity were not independently associated with greater all-cause mortality; there was a 5% increase in long-term risk of prevalent HF with every 1 kg/m<sup>2</sup> increase in BMI among obese and morbidly obese participants; and there was a 5% increase in risk for HF hospitalization with each 1-point increase in BMI greater than 32 kg/m<sup>2</sup>. These findings underscore the significance of the obesity epidemic for AAs, with concerning links to the development of both HF and HF hospitalization. Prevention of obesity in AAs should thus remain a primary public health focus.

### All-cause mortality

Increasing BMI was not associated with increased all-cause mortality in our study and, in fact, was observed to be associated with a 9% lower risk for each additional point of BMI up to 27 kg/m<sup>2</sup>. This breakpoint did not follow the boundaries of traditional BMI categories, such that even some participants in the overweight BMI range had relatively lower risk of death compared to those with normal weight. Previous analyses of large AA cohorts have also paradoxically observed a similar neutral or protective association between BMI and all-cause mortality.[3–9] However, in a recent pooled analysis of these studies, obesity was associated with an increased risk for all-cause mortality in AAs.[23] Our discordant findings between BMI and mortality may relate to the previously described “obesity paradox,” in which individuals with established cardiovascular disease, in particular HF, have better survival relative to their normal-weight counterparts.[24] The mechanisms of the obesity paradox are still under exploration, but result from study design (conditioning on a population with prevalent disease) or physiology (obese individuals having a “metabolic reserve” that helps in tolerating the catabolic effects of systemic disease).[25–29] Because the JHS is community-based, the selection bias that produces potentially distorted



associations between BMI and mortality when restricting to disease-specific populations is not present. Therefore, these results suggest that racial differences may exist with regard to the prognostic utility of BMI values. Further data are necessary to confirm these findings and to explore potential underlying mechanisms.

### Prevalent heart failure

Though BMI was not associated with increased all-cause mortality, the observation of increased HF and HF hospitalization in obese and morbidly obese AAs are important findings. Previous data exploring associations between obesity and HF have primarily been comprised of white populations, and our analysis represents one of the largest to date to assess these associations in AAs.[22, 30–32] The association of obesity and HF in AAs is of particular concern given that nearly one-third of participants were morbidly obese and represented the youngest group in our cohort. This increased risk for HF in the morbidly obese was seen at an earlier time point (exam 2) and persisted to follow up at exam 3. However, the association of obesity with increased prevalent HF was only observed after longer follow-up at exam 3.

In our analysis the overall cohort was predominantly female, with female gender becoming much more common as BMI increased (78.2% [n=1,108] of the morbidly obese). Importantly, we observed no differential effect of BMI on the risk of HF by gender. An increased risk for HF by obese females was suggested previously by results from the Framingham cohort, which again was predominantly white.[22] An increased risk for HF in obese AA women may also have been anticipated with our data, as those AAs (not stratified by body habitus) developing HF from the ARIC cohort were more likely to be women.[33] While gender differences in the risk of HF in AAs may exist, our study suggests that risk associated with BMI is the same for AA men and women.

Moreover, obesity may exert structural and hemodynamic changes that lead to the development of clinical HF.[25] Recent data suggest that obese patients without concomitant metabolic syndrome or those who are “metabolically healthy” may be at decreased risk for HF.[34, 35] To further investigate such potential mediators in the causal pathway between obesity and HF, we performed simplified models separately examining candidate variables of interest. We observed no significant changes in the magnitude and direction of associations of BMI with any of our outcomes in these models. Increasing BMI in AAs was confirmed as an independent risk factor for HF, not attenuated by markers of impaired metabolism or inflammation.

### Heart failure hospitalization

Obesity has also been previously shown to be associated with an increased risk for HF hospitalization in the ARIC cohort and a clinical trial population with impaired glucose tolerance or metabolic syndrome.[36, 37] Obesity, in turn, is a risk factor for longer lengths of stay and increased costs during an episode of acute HF.[38, 39] Morbidly obese AAs in our cohort were relatively younger, potentially compounding the downstream burden associated with higher risk of repeated HF hospitalizations. Of note, the increased risk for HF hospitalization was only observed in the range of BMI greater than 32 kg/m<sup>2</sup>, whereas

AA participants in traditional overweight and a subset of the obese (30 to 32 kg/m<sup>2</sup>) BMI categories had relatively lower risk compared with normal-weight participants. This observation does not detract from our overall findings, given that over 40% of Jackson Heart Study participants had BMI greater than 32 kg/m<sup>2</sup>, but perhaps warrants further appraisal of definitions of BMI categories in AAs. HF hospitalizations represent a major event in the HF disease course, and identification of possible reducible risks such as obesity in patient populations remains important.[40]

### **Clinical and public health implications**

Our data highlight the concerning relationship between obesity and HF and HF hospitalization in AAs, with an incremental observed risk with progressive increases in BMI over specific thresholds. Obesity remains disproportionately high in AAs and obesity prevention and treatment in this population should remain a central focus.[41] Difficulties however remain in finding optimal approaches with regard to addressing the obesity epidemic in AAs.[42] Moreover, further research is also required to define those obese persons with perhaps differential risk (eg with central vs. visceral adiposity) for long-term mortality, HF, and HF hospitalization. The mechanisms underlying the observed “obesity paradox” in cardiovascular disease are complex and require further clarity.

### **Limitations**

This was a retrospective analysis from a community cohort of AAs in the southern United States. Other measured and unmeasured variables may have influenced the results. As an example, physical activity level or fitness have been shown to impact the association of obesity with HF and survival.[43, 44] Our definition of HF may not have captured all patients with clinical HF; however, our definition has previously been used and validated in the ARIC and Jackson Heart Study data sets. In addition, consistent clinical data (eg, follow-up echocardiograms) was unavailable to define the type of HF (ie HF with preserved ejection fraction vs. HF with reduced ejection fraction). The discontinuity between clinical data collection at exam 1 (between 2000 and 2004) and the start of HF hospitalization surveillance (2005) may have resulted in an underestimation of the effect of BMI on HF hospitalization. Finally, BMI was examined at a single time point and BMI may have been dynamic during study participation. These subsequent changes in BMI (either increased or decreased) may have affected the observed associations with outcomes. However, the distribution of BMI categories at exams 2 and 3 was similar to baseline, and the median net change in BMI from baseline was 0.35 kg/m<sup>2</sup> at exam 2 and 0.48 kg/m<sup>2</sup> at exam 3.

### **Conclusions**

Obesity and morbid obesity are common in African Americans and were associated with increased prevalent HF and HF hospitalization. Obesity remains a major public health concern and should be considered as an important risk factor for long-term morbidity in African American populations and a potential target for intervention.

### **Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.



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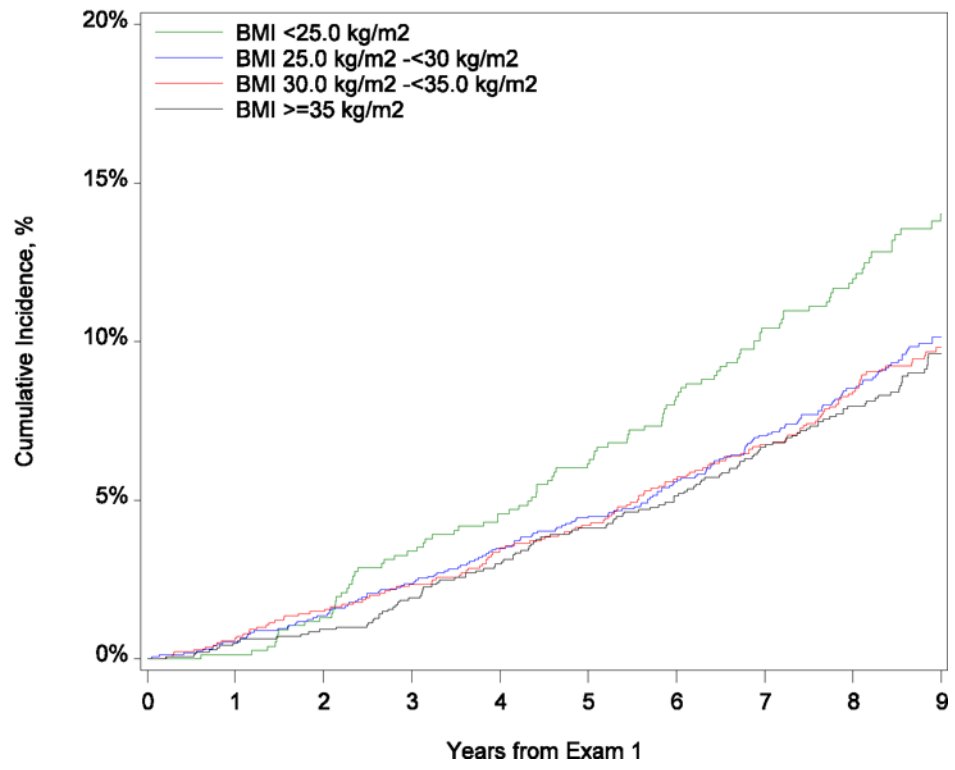
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### Highlights

- The relationship between obesity and health outcomes such as mortality and heart failure (HF) in African Americans was further explored from the Jackson Heart Study
- Increasing body mass index (BMI) was not associated with increased risk for all-cause mortality in African Americans
- However, increasing BMI was associated with increasing risk for prevalent HF and HF hospitalization in African Americans
- Obesity remains a major public health concern and should be considered as an important risk factor for long-term morbidity in African American populations and a potential target for intervention

A



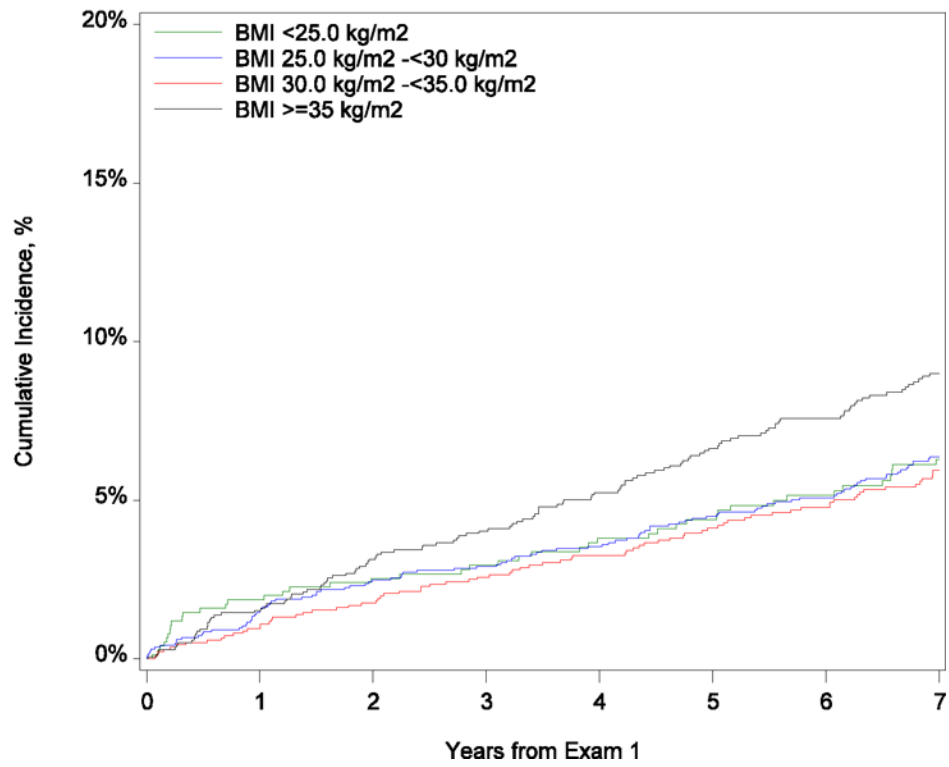
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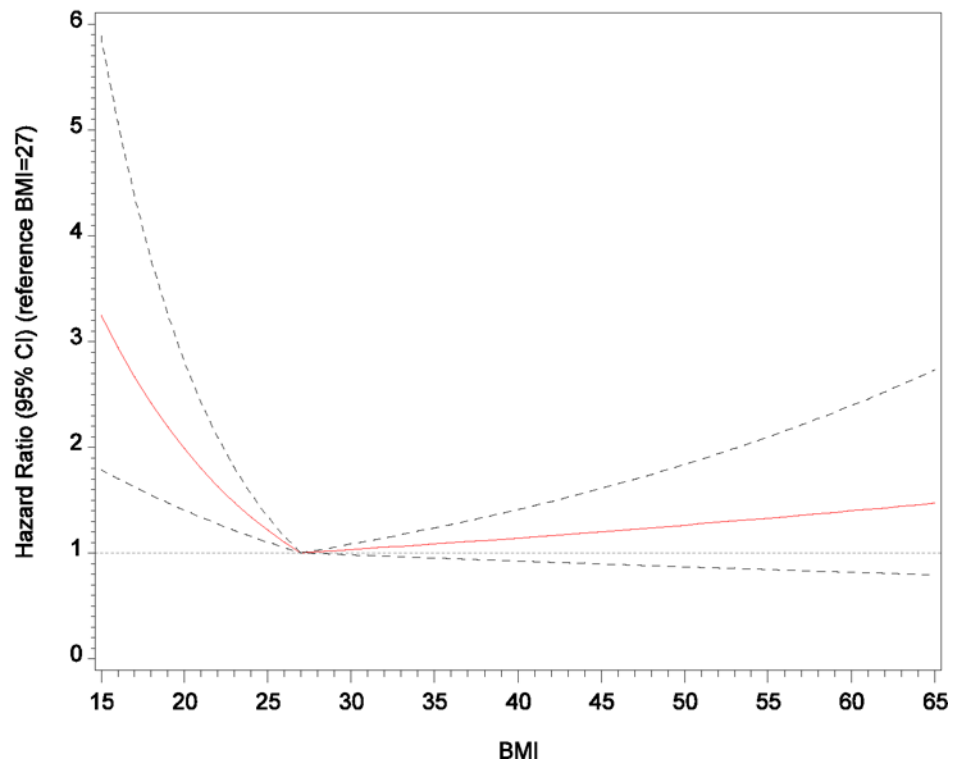
**B**



**Figure 1.** Cumulative Incidence of (A) Mortality at 9 Years and (B) Heart Failure Hospitalization at 9 Years by Body Mass Index Category



A

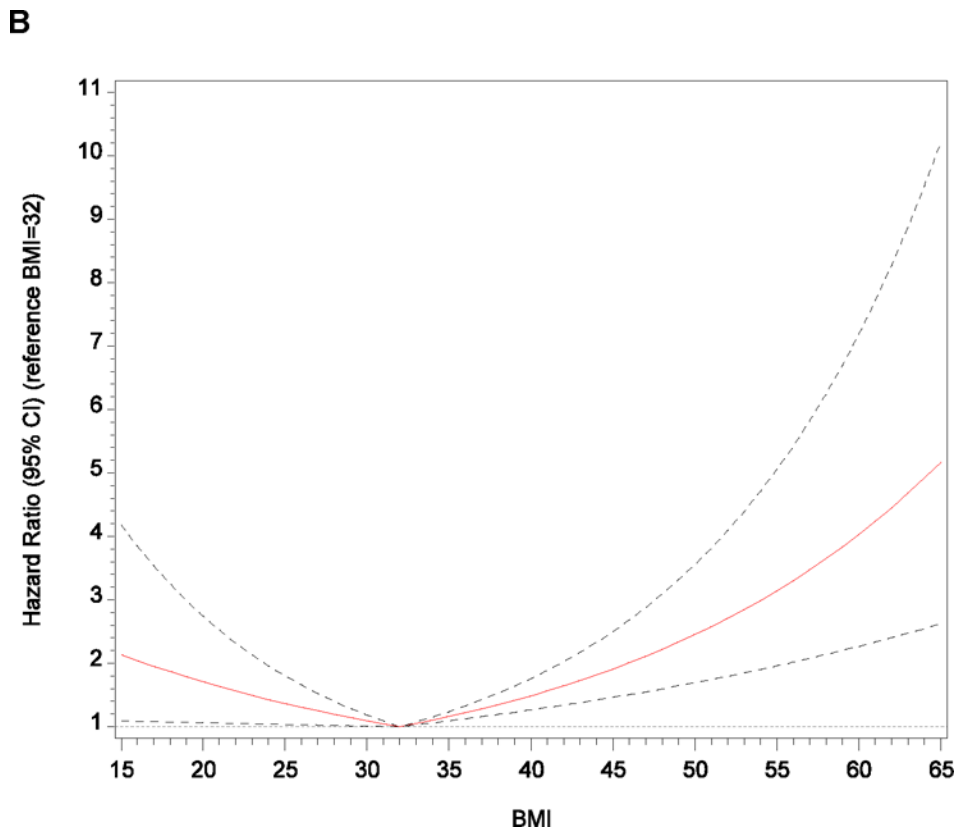


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**Figure 2.** Adjusted Relationships Between Body Mass Index and (A) All-Cause Mortality and (B) Heart Failure Hospitalization After Application of Linear Splines

Abbreviation: BMI, body mass index.

Note: We used information gleaned from restricted cubic spline exploratory analyses to develop linear spline models with knots selected according to optimal model fit determined by the minimum Akaike information criterion. We selected knots at body mass index of 27 kg/m<sup>2</sup> for all-cause mortality and 32 kg/m<sup>2</sup> for heart failure hospitalization, which we then used as reference categories (ie, hazard ratio of 1.00) for linear spline graphs.

**Table 1**

**Baseline Characteristics of the Study Population**

Variable	Normal <sup>d</sup>	Overweight <sup>d</sup>	Obese <sup>d</sup>	Morbidly Obese <sup>d</sup>	P Value
No. of participants	769	1701	1406	1416	
Age, median (IQR)	55.2 (43.9–66.5)	58.1 (46.6–65.9)	56.3 (46.6–64.9)	53.5 (44.1–63.0)	<.001
Men, No. (%)	356 (46.3)	777 (45.7)	489 (34.8)	308 (21.8)	<.001
Medical history, No. (%)					
Atrial fibrillation	1 (0.1)	9 (0.5)	5 (0.4)	3 (0.2)	.32
Chronic lung disease	61 (7.9)	105 (6.2)	90 (6.4)	125 (8.8)	.02
Diabetes mellitus	58 (7.5)	298 (17.5)	349 (24.8)	445 (31.4)	<.001
Heart failure	23 (3.0)	71 (4.2)	106 (7.5)	196 (13.8)	<.001
Hypertension	357 (46.4)	975 (57.3)	896 (63.7)	954 (67.4)	<.001
Myocardial infarction	36 (4.7)	92 (5.4)	87 (6.2)	73 (5.2)	.46
Current smoker	179 (23.3)	214 (12.6)	154 (11.0)	143 (10.1)	<.001
Previous smoker	138 (17.9)	349 (20.5)	286 (20.3)	246 (17.4)	.08
Stroke	33 (4.3)	71 (4.2)	67 (4.8)	62 (4.4)	.88
Physical examination, median (IQR)					
Weight, kg	66.0 (60.3–71.5)	79.8 (72.9–86.6)	91.5 (84.4–99.6)	110.0 (100.5–124.0)	<.001
Waist circumference, cm	82.0 (76.0–87.0)	94.0 (88.0–99.0)	103.0 (97.0–109.0)	116.5 (107.0–127.0)	<.001
Neck circumference, cm	35.0 (33.0–38.0)	38.0 (35.0–40.0)	39.0 (36.0–42.0)	40.0 (38.0–43.0)	<.001
Systolic blood pressure, mm Hg	122.0 (112.0–136.0)	124.0 (114.0–136.0)	125.0 (116.0–137.0)	126.0 (116.0–137.0)	<.001
Laboratory test results, median (IQR)					
eGFR, mL/min/1.73 m <sup>2</sup>	88.3 (77.6–99.4)	85.3 (75.6–94.8)	85.9 (75.1–96.6)	86.5 (75.9–97.3)	<.001
Glucose, mg/dL	88.0 (83.0–93.0)	91.0 (85.0–99.0)	93.0 (87.0–103.0)	94.0 (87.0–107.0)	<.001
Hemoglobin A <sub>1c</sub> , %	5.4 (5.1–5.7)	5.6 (5.3–6.0)	5.7 (5.4–6.2)	5.8 (5.5–6.5)	<.001
Triglycerides, mg/dL	74.0 (52.0–103.0)	90.0 (63.0–123.0)	98.0 (73.0–138.0)	94.0 (72.0–134.0)	<.001
HDL cholesterol, mg/dL	55.0 (45.0–67.0)	49.0 (41.0–60.0)	48.0 (40.0–57.0)	49.0 (41.0–57.0)	<.001
LDL cholesterol, mg/dL	119.0 (95.0–140.0)	124.0 (103.0–150.0)	124.0 (103.0–148.0)	124.0 (101.0–147.0)	<.001
High-sensitivity C-reactive protein, mg/dL	0.1 (0.0–0.3)	0.2 (0.1–0.4)	0.3 (0.1–0.6)	0.5 (0.3–0.9)	<.001

Variable	Normal <sup>d</sup>	Overweight <sup>d</sup>	Obese <sup>d</sup>	Morbidly Obese <sup>d</sup>	P Value
Uric acid, mg/dL	4.8 (3.8–5.7)	5.3 (4.2–6.4)	5.5 (4.5–6.7)	5.7 (4.8–6.8)	< .001
Baseline echocardiography and ECG					
Ejection fraction, mean (SD), %	61.6 (7.3)	61.7 (7.8)	62.1 (7.4)	62.4 (7.3)	.09
Ejection fraction, median (IQR), %	65.0 (55.0–65.0)	65.0 (55.0–65.0)	65.0 (55.0–65.0)	65.0 (55.0–65.0)	.09
LVEF < 40%, No. (%)	8 (1.0)	20 (1.2)	10 (0.7)	11 (0.8)	.51
Left ventricular hypertrophy, No. (%)	25 (3.3)	103 (6.1)	106 (7.5)	188 (13.3)	< .001
Left ventricular dimension, median (IQR), cm	47.4 (44.3–49.9)	48.3 (45.3–50.8)	48.3 (45.8–50.9)	48.9 (46.5–51.9)	< .001
Medications, No. (%)					
β-Blocker	49 (6.4)	165 (9.7)	160 (11.4)	157 (11.1)	.001
Missing	57 (7.4)	113 (6.6)	108 (7.7)	105 (7.4)	.70
Calcium channel blocker	84 (10.9)	310 (18.2)	290 (20.6)	304 (21.5)	< .001
Missing	54 (7.0)	103 (6.1)	110 (7.8)	96 (6.8)	.28
Diuretic	99 (12.9)	323 (19.0)	339 (24.1)	459 (32.4)	< .001
Missing	52 (6.8)	107 (6.3)	99 (7.0)	88 (6.2)	.79
Statin	53 (6.9)	202 (11.9)	194 (13.8)	152 (10.7)	< .001
Missing	58 (7.5)	108 (6.3)	107 (7.6)	105 (7.4)	.49
Insulin	14 (1.8)	71 (4.2)	102 (7.3)	139 (9.8)	< .001
Missing	59 (7.7)	113 (6.6)	112 (8.0)	103 (7.3)	.54
Loop diuretic	15 (2.0)	58 (3.4)	74 (5.3)	159 (11.2)	< .001
Missing	58 (7.5)	118 (6.9)	114 (8.1)	101 (7.1)	.63
ACE inhibitor or ARB	86 (11.2)	243 (14.3)	247 (17.6)	307 (21.7)	< .001
Missing	56 (7.3)	99 (5.8)	106 (7.5)	88 (6.2)	.20
Anti-platelet agent	10 (1.3)	28 (1.6)	24 (1.7)	17 (1.2)	.63
Missing	59 (7.7)	118 (6.9)	116 (8.3)	109 (7.7)	.59
Digoxin	12 (1.6)	20 (1.2)	20 (1.4)	27 (1.9)	.41
Missing	57 (7.4)	118 (6.9)	114 (8.1)	111 (7.8)	.63

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BMI, body mass index; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; and LVEF, left ventricular ejection fraction.

<sup>d</sup>Normal indicates BMI < 25 mg/dL; overweight, BMI 25 to < 30 mg/dL; obese, 30 to < 35 mg/dL; and morbidly obese, ≥ 35 mg/d

**Table 2**

Associations Between BMI and All-Cause Mortality, Heart Failure, and Heart Failure Hospitalization

Outcome <sup>a</sup>	Unadjusted Estimate	P Value	Adjusted Estimate <sup>b</sup>	P Value
All-cause mortality				
BMI as a continuous variable (n = 5292)	0.99 (0.98–1.00)	.08	0.99 (0.98–1.01)	.41
BMI by category				
< 25 kg/m <sup>2</sup> (n = 769)	1.00 [Reference]		1.00 [Reference]	
25 to < 30 kg/m <sup>2</sup> (n = 1701)	0.70 (0.55–0.90)	.006	0.66 (0.51–0.86)	.002
30 to < 35 kg/m <sup>2</sup> (n = 1406)	0.68 (0.53–0.89)	.004	0.70 (0.52–0.93)	.01
35 kg/m <sup>2</sup> (n = 1416)	0.66 (0.51–0.85)	.002	0.66 (0.49–0.89)	.007
Prevalent heart failure at exam 2				
BMI as a continuous variable (n = 3896)	1.06 (1.04–1.07)	< .001	1.06 (1.04–1.08)	< .001
BMI by category				
< 25 kg/m <sup>2</sup> (n = 554)	1.00 [Reference]		1.00 [Reference]	
25 to < 30 kg/m <sup>2</sup> (n = 1317)	1.29 (0.66–2.53)	.45	1.38 (0.72–2.65)	.33
30 to < 35 kg/m <sup>2</sup> (n = 1061)	1.95 (1.01–3.77)	.046	1.68 (0.87–3.24)	.12
35 kg/m <sup>2</sup> (n = 964)	4.26 (2.29–7.94)	< .001	3.74 (2.00–7.03)	< .001
Prevalent heart failure at exam 3				
BMI as a continuous variable (n = 3559)	1.05 (1.04–1.07)	< .001	1.05 (1.03–1.06)	< .001
BMI by category				
< 25 kg/m <sup>2</sup> (n = 496)	1.00 [Reference]		1.00 [Reference]	
25 to < 30 kg/m <sup>2</sup> (n = 1204)	1.48 (0.78–2.77)	.23	1.53 (0.83–2.83)	.18
30 to < 35 kg/m <sup>2</sup> (n = 969)	2.59 (1.41–4.77)	.002	2.27 (1.23–4.21)	.009
35 kg/m <sup>2</sup> (n = 890)	4.53 (2.51–8.16)	< .001	3.97 (2.20–7.17)	< .001
Heart failure hospitalization				
BMI as a continuous variable (n = 5184)	1.03 (1.01, 1.04)	< .001	1.02 (1.01, 1.04)	.007
BMI by category				
< 25 kg/m <sup>2</sup> (n = 755)	1.00 [Reference]		1.00 [Reference]	
25 to < 30 kg/m <sup>2</sup> (n = 1664)	1.01 (0.71–1.44)	.96	0.79 (0.54–1.14)	.20
30 to < 35 kg/m <sup>2</sup> (n = 1376)	0.93 (0.64–1.35)	.71	0.68 (0.46–1.02)	.06
35 kg/m <sup>2</sup> (n = 1389)	1.44 (1.02–2.04)	.04	0.97 (0.66–1.44)	.89

Abbreviations: BMI, body mass index; HR, hazard ratio; RR, risk ratio.

<sup>a</sup>Estimates for all-cause mortality and heart failure hospitalization are expressed as hazard ratio (95% CI). Estimates for prevalent heart failure are expressed as risk ratio (95% CI).<sup>b</sup>The multivariable models were adjusted for age, sex, prior myocardial infarction, hypertension, prior stroke, diabetes mellitus, chronic lung disease, smoking status, systolic blood pressure, pulse, sodium, estimated glomerular filtration rate, hemoglobin, glucose, high-sensitivity C-reactive protein, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, left ventricular ejection fraction, left ventricular hypertrophy, left ventricular diameter, beta-blocker, angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker, statin, antiplatelet agent, and missing medication status. The multivariable all-cause mortality and heart failure hospitalization models were also adjusted for heart failure based on modified Gothenburg criteria at exam 1.